Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

GYNECOLOGY

Association of laparoscopically-confirmed endometriosis with long COVID-19: a prospective cohort study

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BACKGROUND: Women are at greater risk than men of developing chronic inflammatory conditions and "long COVID." However, few gynecologic health risk factors for long COVID-19 have been identified. Endometriosis is a common gynecologic disorder associated with chronic inflammation, immune dysregulation, and comorbid presentation with autoimmune and clotting disorders, all of which are pathophysiological mechanisms proposed for long COVID-19. Therefore, we hypothesized that women with a history of endometriosis may be at greater risk of developing long COVID-19.

OBJECTIVE: This study aimed to investigate the association between history of endometriosis before SARS-CoV-2 infection and risk of long COVID-19.

STUDY DESIGN: We followed 46,579 women from 2 ongoing prospective cohort studies—the Nurses' Health Study II and the Nurses' Health Study 3—who participated in a series of COVID-19-related surveys administered from April 2020 to November 2022. Laparoscopic diagnosis of endometriosis was documented prospectively in main cohort questionnaires before the pandemic (1993—2020) with high validity. SARS-CoV-2 infection (confirmed by antigen, polymerase chain reaction, or antibody test) and long-term COVID-19 symptoms (≥4 weeks) defined by the Centers for Disease Control and Prevention were self-reported during follow-up. Among individuals with SARS-CoV-2 infection, we fit Poisson regression models to assess the associations between endometriosis and risk of long COVID-19 symptoms, with adjustment for potential confounding variables (demographics, body mass index, smoking status, history of infertility, and history of chronic diseases).

RESULTS: Among 3650 women in our sample with self-reported SARS-CoV-2 infections during follow-up, 386 (10.6%) had a history of endometriosis with laparoscopic confirmation, and 1598 (43.8%) reported experiencing long COVID-19 symptoms. Most women were non-Hispanic White (95.4%), with a median age of 59 years (interquartile range, 44—65). Women with a history of laparoscopically-confirmed endometriosis had a 22% greater risk of developing long COVID-19 (adjusted risk ratio, 1.22; 95% confidence interval, 1.05—1.42) compared with those who had never been diagnosed with endometriosis. The association was stronger when we defined long COVID-19 as having symptoms for ≥8 weeks (risk ratio, 1.28; 95% confidence interval, 1.09—1.50). We observed no statistically significant differences in the relationship between endometriosis and long COVID-19 by age, infertility history, or comorbidity with uterine fibroids, although there was a suggestive trend indicating that the association may be stronger in women aged <50 years (<50 years: risk ratio, 1.37; 95% confidence interval, 1.00—1.88; ≥50 years: risk ratio, 1.19; 95% confidence interval, 1.01—1.41). Among persons who developed long COVID-19, women with endometriosis reported on average 1 additional long-term symptom compared with women without endometriosis.

CONCLUSION: Our findings suggest that those with a history of endometriosis may be at modestly increased risk for long COVID-19. Healthcare providers should be aware of endometriosis history when treating patients for signs of persisting symptoms after SARS-CoV-2 infection. Future studies should investigate the potential biological pathways underlying these associations.

Key words: endometriosis, inflammation, laparoscopically-confirmed endometriosis, long COVID, post-COVID-19 conditions, SARS-CoV-2

Introduction

Post-COVID-19 conditions, also known as "long COVID," are characterized as having persistent or emerging symptoms related to COVID-19 at ≥4 weeks after SARS-CoV-2 infection.[1,2] Long COVID-19 can have manifestations in multiple systems, with common symptoms ranging from fatigue, heart palpitations, depression, muscle pain, and memory issues, which individually or comorbidly can impair daily function.[3,4] Long COVID-19 is estimated to affect 20% to 40% of individuals infected with SARS-CoV-2.[2,5] The prevalence was higher, reaching 50%, among those who were infected by earlier strains, unvaccinated against COVID-19, or hospitalized because of COVID-19.[6—8] With ongoing waves of SARS-CoV-2 infections, the growing number of long COVID-19 patients indicates considerable affliction, and may impose a substantial burden on health systems. However, long COVID-19 remains poorly understood, and the US government has announced a national research plan to determine the etiology, identify high-risk groups, and develop targeted treatments for long COVID-19.[9]

Endometriosis is a common, often chronic inflammatory disease affecting approximately 10% of women of reproductive age.[10,11] Associated symptoms include chronic pelvic pain, dysmenorrhea, and infertility.[10,11] Female sex is a well-established risk factor for long COVID-19, but there is a paucity of research identifying female-specific risk

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AJOG at a Glance

Why was this study conducted?

The associations of history of endometriosis with risk of long COVID-19 and daily life impairment related to long COVID-19 are not established.

Key findings

Women who had a history of laparoscopically-confirmed endometriosis had 1.22-fold increased risk of long COVID-19 (≥4 weeks of symptoms) compared with women without endometriosis. The association between endometriosis and long COVID-19 was moderately stronger when defining long COVID-19 as symptoms lasting for ≥8 weeks (1.28-fold) or having ongoing symptoms at the time of long COVID-19 assessment (1.32-fold). Among women who developed long COVID-19, history of endometriosis was associated with reporting on average 1 more long COVID-19 symptom, and with daily life impairment owing to long COVID-19.

What does this add to what is known?

Healthcare providers should consider informing patients with endometriosis of their increased risk of long COVID-19, and of the benefits of preventive measures such as vaccines.

factors for long COVID-19.[3,12–15] Inflammation, blood clotting disorders, and autoimmunity—the mechanisms proposed for the development of long COVID-19—have all been implicated in the pathophysiology of endometriosis.[3,10,16–18] One retrospective study of nonhospitalized persons with SARS-CoV-2 infection suggested that those with endometriosis may have higher risk for long COVID-19.[14] However, whether the association may be explained by COVID-19 hospitalization, behavioral factors, pandemic effects independent of infection, or other comorbidities (eg, infertility,[19] hypertension[20]) is unknown. Further, no studies have investigated the daily life impairment because of long-term COVID-19 symptoms among women with endometriosis.

In this study, we prospectively investigated the association between history of laparoscopically-confirmed endometriosis and risk of long COVID-19 among individuals infected with SARS-CoV-2. In addition, among persons who developed long COVID-19, we examined whether women with endometriosis reported more long-term symptoms, a distinct pattern of long-term symptoms, or more severe daily life impairment related to long COVID-19 compared with those without endometriosis.

Materials and Methods

Study design

Participants were drawn from 2 prospective cohorts: the Nurses' Health Study II (NHSII) and the Nurses' Health Study 3 (NHS3).[21] The NHSII was established in 1989, when 116,429 registered nurses aged 25 to 42 years residing in the United States were enrolled. Biennial follow-up questionnaires are mailed to collect health information. The NHS3, a web-based open cohort, was launched in 2010 and has recruited >49,000 female nurses and nursing students born after January 1, 1965, living across North America, with twice-yearly follow-up.

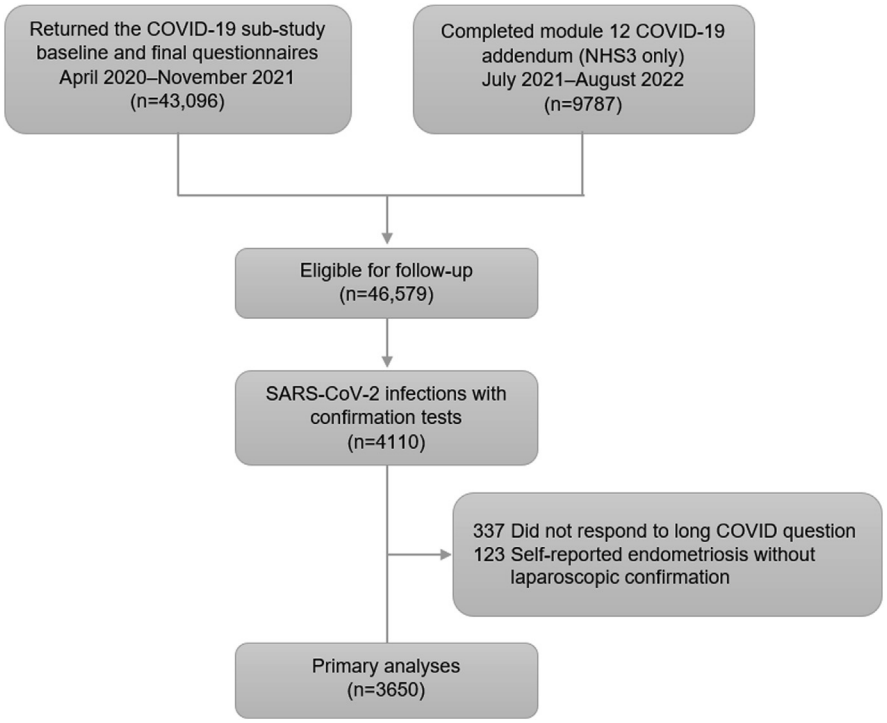
During April and May 2020, participants who returned the most recent main cohort follow-up questionnaire were invited to participate in a series of COVID-19-related surveys (COVID-19 substudy) that collected additional health information during the pandemic. Of 86,568 invited, 51,312 (59.3%) returned the first COVID-19-related questionnaire by August 2020 (termed "baseline" henceforth). Six-monthly and then quarterly follow-up questionnaires were administered through November 2021. In addition, from July 2021 to August 2022, NHS3 participants who were in the 12th follow-up cycle (module [MOD] 12) also completed an addendum about COVID-19 (not mutually exclusive with the COVID-19 substudy participants).

For the current study, we included 46,579 women who: (1) returned both the baseline and final (administered 12 months after baseline) COVID-19 substudy questionnaires, or (2) returned the MOD12 questionnaire (Figure 1). The study was approved by the Institutional Review Board of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. The return of questionnaires implied informed consent. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Ascertainment of endometriosis

In both cohorts, participants were asked whether they had a history of physician-diagnosed endometriosis, and if so, whether the diagnosis was confirmed by laparoscopy, the clinical gold standard for endometriosis diagnosis.[22] These series of questions were asked on 1993–2017 biennial questionnaires for NHSII participants, and on MOD1 to MOD12 questionnaires for NHS3 participants. Self-reported endometriosis was validated in 1994 (n=200) and 2011 (n=711), and a diagnosis of endometriosis was confirmed in the medical records of 95% and 100% of women reporting laparoscopically-confirmed endometriosis in the first and second validation studies, respectively; however, a diagnosis of endometriosis was only confirmed in 56% of women reporting endometriosis without laparoscopic confirmation.[23] Therefore, for the primary analyses, we defined exposure to endometriosis as those with laparoscopic confirmation before the COVID-19 pandemic (March 2020), and the nonexposed group comprised women who had never been diagnosed with endometriosis (excluding those with

FIGURE 1
Flow chart of study design, NHSII (1989–2021) and NHS3 (2010–2022)



NHSII, Nurses' Health Study II; *NHS3*, Nurses' Health Study 3.

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self-reported endometriosis but without surgical confirmation).

Ascertainment of SARS-CoV-2 infection and long COVID-19

The details of ascertainment of long COVID-19 in this cohort have been previously published.[24] Briefly, date of a positive SARS-CoV-2 diagnostic test (antigen, polymerase chain reaction, or antibody) since March 1, 2020 was self-reported on each of the COVID-19 substudy questionnaires and on MOD12. On the final COVID-19 substudy questionnaire and MOD12, participants were asked whether they had any COVID-19 symptoms lasting for >4 weeks. If so, participants were asked to report COVID-19-related symptoms that they experienced, including fatigue, shortness of breath or difficulty breathing, persistent cough, muscle/joint/chest pain, smell/taste problems, confusion/disorientation/"brain fog," memory issues, depression/anxiety/changes in mood, headache, intermittent fever, heart palpitations, rash/blisters/welts, mouth or tongue ulcers, or other symptoms. Among COVID-19 substudy participants, those with self-reported long COVID-19 were also asked: (1) the duration of symptoms; (2) whether the symptoms were ongoing at the time of completing the questionnaire; and (3) how often the symptoms prevented them from carrying out daily activities (never, occasionally, often, usually, or always).

For primary analyses, we defined long COVID-19 by the Centers for Disease Control and Prevention definition of having ≥1 symptoms for ≥4 weeks after infection.[1,2] In secondary analyses, we defined long COVID-19 as having ≥1 symptoms for ≥8 weeks,[25] and we restricted the long COVID-19 case group to those who had ongoing symptoms at the time of completing the questionnaire to reduce potential recall bias.

Covariates

Birthdate, height, and race were self-reported at cohort enrollment. Marital status and educational attainment of partner were collected in 1999 for NHS2 and in MOD1 for NHS3 as a weak proxy for socioeconomic status, given that these cohorts of nursing professionals have more homogeneous educational attainment than the general population. Weight and cigarette smoking status were collected on the most recent prepandemic main cohort questionnaires (2017 for NHSII and the most recent follow-up module for NHS3). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. History of infertility (defined as ever having failure to achieve pregnancy after 12 months of attempts), ultrasound- or hysterectomy-confirmed uterine fibroids, diabetes mellitus, asthma, hypertension, high cholesterol, and cancer were derived from all main cohort questionnaires. Hospitalization(s) because of COVID-19 were self-reported on each of the COVID-19 substudy follow-up questionnaires and on MOD12. COVID-19 vaccination (date of first dose) was queried on the second and third quarterly COVID-19 substudy follow-up questionnaires and on MOD12. Among COVID-19 substudy participants, frontline healthcare worker status (ie, actively working at a healthcare site), depressive symptoms (measured by the Patient Health Questionnaire-2),[26] anxiety symptoms (measured by Generalized Anxiety Disorder 2-item),[26] and worry about COVID-19[27] were queried at baseline.

Statistical analysis

Among 4110 participants with self-reported SARS-CoV-2 infections during follow-up, we excluded 337 women who did not respond to the long COVID-19 question. We first compared the prevalence of sociodemographic and behavioral factors, prepandemic comorbidities, and mental health well-being on the first COVID-19-related survey according to history of laparoscopically-confirmed endometriosis. Poisson regression models were used to assess the associations between endometriosis and long COVID, adjusting for age (at baseline), race, cigarette smoking status, BMI, and

history of comorbidities. Missingness for each variable was <5%. Indicator variables were used for any missing covariate information for categorical variables. Missing values of continuous variables were replaced with the median.[28]

Because women with concurrent uterine fibroids or infertility may have different clinical presentations of endometriosis (eg, women with infertility or fibroids may be "asymptomatic" and only receive diagnoses during infertility checkups/fibroid evaluation), and hence potentially different risk profiles, we investigated whether the associations with long COVID-19 differ among those with history of endometriosis and additional reproductive disorders.[29] To test heterogeneity between groups, we conducted Wald tests for differential associations for pairwise comparisons.[30] In addition, we examined the potential for effect modification by age (<50 vs ≥50 years). Multiplicative interaction was calculated by adding a cross-product term in the model.

Finally, among women with self-reported long COVID-19, we compared the documented individual symptoms between those with and those without endometriosis. *P* values for differences across categories were calculated using chi-square tests. We also fit Poisson regression models to estimate the associations between endometriosis and daily life impairment owing to long COVID-19.

We conducted 9 additional sensitivity analyses. First, we included all self-reported physician-diagnosed endometriosis in the exposed group (n=509), regardless of laparoscopic confirmation. Second, we included 1475 self-presumed SARS-CoV-2 infections without a confirmation test among the SARS-CoV-2 cases. Third, to distinguish long COVID-19 from chronic symptoms that could be associated with endometriosis, we excluded 132 women reporting only fatigue, depression, headache, or muscle pain as their long COVID-19 symptoms. Fourth, in a subsample of 3155 participants with healthcare worker status and psychological distress information assessed at baseline, we additionally adjusted for these pandemic-related factors. Fifth, we additionally adjusted for hospitalization owing to COVID-19 to account for severity of acute phase disease. Sixth, because COVID-19 vaccination may reduce the risk of long COVID,[31] we additionally adjusted for history of vaccination at the time of infection. Seventh, we restricted analysis to 2292 SARS-CoV-2 infections dated before the authorization of the first COVID-19 vaccine in the United States (December 11, 2020) in individuals aged ≥16 years.[32] Eighth, to reduce the variation in main SARS-CoV-2 strains, we excluded 156 participants whose date of a positive infection test was after November 1, 2021 (after the emergence of the Omicron variant).[33] Ninth, we used several methods to address missing outcome and covariates (eg, multiple imputation, complete case analysis, and treating all missing outcome as cases or noncases).[34] All analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided.

Results

We documented 3650 persons with SARS-CoV-2 infections during follow-up (excluding 123 self-reported endometriosis cases without surgical confirmation). Among these, 95.4% (n=3481) were non-Hispanic White, with a median age of 59 years (interquartile range, 44−65; range, 22−75), and 386 (10.6%) had a history of endometriosis. Compared with women without a history of endometriosis, women reporting a history of endometriosis were older, more likely to be non-Hispanic White, less likely to be unpartnered, more likely to have a history of comorbidity (including asthma, hypertension, high cholesterol, uterine fibroids, and infertility), and less likely to be a frontline healthcare worker, and had higher BMI and higher levels of psychological distress at baseline (greater score of depressive and anxiety symptoms and more likely to be worried about COVID-19; Table 1).

During follow-up, 1598 women (43.8%) developed long COVID-19 (≥4 weeks of symptoms), and 1353 (37.0%) reported having symptoms at ≥8 weeks. The most common long COVID symptoms were fatigue (53.6%; n=857), smell or taste problems (42.5%; n=679), shortness of breath (26.8%; n=428), confusion/disorientation/"brain fog" (24.5%; n=391), and memory issues (22.4%; n=358). Among 1334 participants who developed long COVID-19 and had provided daily function information, 745 (55.8%) had at least occasional daily life impairment related to long COVID-19.

History of endometriosis was associated with greater risk of long COVID-19 (risk ratio [RR], 1.26; 95% confidence interval [CI], 1.09−1.46) (Table 2, model 1), adjusting for demographic factors. The risk estimates remained unchanged after additionally adjusting for behavioral factors (Table 2, model 2), and were negligibly attenuated after further adjustment for history of comorbidities (RR, 1.22; 95% CI, 1.05−1.42) (Table 2, model 3). The associations were stronger when we defined long COVID-19 as having ≥8 weeks of symptoms (RR, 1.28; 95% CI, 1.09−1.50) or as having ongoing symptoms (RR, 1.32; 95% CI, 1.11−1.58).

Women with a history of endometriosis who also had histories of uterine fibroids and/or infertility were at higher risk of long COVID-19 compared with those with endometriosis alone (Table 3). However, we did not observe a meaningful difference between exposure groups (*P* values=.73 and.55 in pairwise tests). In addition, although the association between endometriosis and long COVID-19 was considerably stronger among women aged <50 years (RR, 1.37; 95% CI, 1.00−1.88) (Supplemental Table 1) compared with older participants (RR, 1.19; 95% CI, 1.01−1.41), age was not a statistically significant effect modifier (*P* interaction=.39).

Results were very similar in sensitivity analyses including all self-reported endometriosis regardless of laparoscopic confirmation; including self-report of SARS-CoV-2 infections without a confirmation test; excluding participants reporting only fatigue, depression, headache, or muscle pain

as their long COVID-19 symptoms; in models additionally adjusted for hospitalization owing to COVID-19, pandemic-related stress, or vaccination status at the time of infection; in models that restricted analysis to SARS-CoV-2 infections before vaccine authorization or emergence of the Omicron variant; or after multiple imputation (Supplemental Tables 2 and 3).

Among women who developed long COVID-19, we compared the prevalence of individual long COVID-19 symptoms by history of endometriosis. Women with a history of endometriosis had a higher percentage of reporting each of the long COVID-19–related symptoms (Figure 2). Notably, they reported, on average, 1 more symptom compared with those never diagnosed with endometriosis (mean [standard deviation] number of symptoms: with endometriosis, 3.4 [2.3]; without endometriosis, 2.6 [1.9]). Endometriosis may also be associated with increased risk of daily life impairment resulting from long COVID-19, although the 95% CI crossed the null (fully adjusted RR, 1.17; 95% CI, 0.96–1.43).

Comment

Principal findings

In this prospective cohort study, among individuals infected with SARS-CoV-2, we found that history of laparoscopically-confirmed endometriosis was associated with 22% higher risk of developing long COVID-19. The associations were not attenuated when accounting for pandemic-related stress or acute phase disease severity, and did not differ by history of endometriosis plus uterine fibroids or infertility. The results indicated that the association between a history of endometriosis and long COVID-19 was stronger in participants aged <50 years than in those aged ≥50 years; however, this difference was not statistically significant. Among participants with self-reported long COVID-19, women with a history of endometriosis reported more long-term symptoms and may have a greater risk of daily life impairment owing to long COVID-19.

TABLE 1
Age-adjusted baseline (April 2020–August 2020) characteristics by history of prepandemic laparoscopically-confirmed endometriosis among participants with self-reported positive SARS-CoV-2 test during follow-up (Nurses' Health Study II [1989–2021] and Nurses' Health Study 3 [2010–2022]), N = 3650

	History of laparoscopically-confirmed endometriosis	
	No	Yes
Characteristics	n=3264	n=386
Age, median (IQR), y[a]	54.6 (12.9)	58.9 (10.2)
Non-Hispanic White, n (%)	3107 (95.2)	372 (96.4)
Partner's educational attainment, n (%)		
High school or lower	388 (11.9)	50 (13.0)
College	1311 (40.2)	164 (42.5)
Graduate school	550 (16.8)	67 (17.3)
Unpartnered	931 (28.5)	93 (24.1)
Smoking status, n (%)		
Never	2319 (71.1)	273 (70.8)
Past	844 (25.9)	97 (25.2)
Current	93 (2.8)	14 (3.6)
BMI, n (%), kg/m^2		
<18.5	37 (1.2)	6 (1.6)
18.5–24.9	1115 (34.6)	109 (28.5)
25.0–29.9	946 (29.4)	127 (33.3)
≥30.0	1121 (34.8)	140 (36.7)
Physician previously diagnosed with:		
Diabetes mellitus, n (%)	165 (5.1)	17 (4.5)
Asthma, n (%)	426 (13.1)	69 (17.9)
Hypertension, n (%)	647 (19.8)	90 (23.3)
High cholesterol, n (%)	884 (27.1)	113 (29.2)
Cancer, n (%)	143 (4.4)	18 (4.7)
Uterine fibroids, n (%)[b]	643 (19.7)	141 (36.6)
Infertility, n (%)[c]	644 (19.7)	161 (41.8)
Hospitalization owing to COVID-19, n (%)	129 (3.9)	22 (5.7)
Vaccinated against COVID-19 (first dose) at time of infection, n (%)	422 (12.9)	56 (14.6)
Characteristics at COVID-19 substudy baseline (April 2020–Aug. 2020)		
Frontline healthcare worker, n (%)[d,e]	1611 (57.1)	186 (53.0)
Depressive symptoms (PHQ-2), mean (SD)[d]	1.1 (1.4)	1.3 (1.6)
Probable depression (PHQ-2 ≥3), n (%)	337 (12.0)	64 (18.2)
Anxiety symptoms (GAD-2), mean (SD)[d]	1.4 (1.5)	1.6 (1.6)
Probable anxiety (GAD-2 ≥3), n (%)	559 (19.9)	90 (25.6)

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TABLE 1
Age-adjusted baseline (April 2020–August 2020) characteristics by history of prepandemic laparoscopically-confirmed endometriosis among participants with self-reported positive SARS-CoV-2 test during follow-up (Nurses' Health Study II [1989–2021] and Nurses' Health Study 3 [2010–2022]), N = 3650 *(continued)*

	History of laparoscopically-confirmed endometriosis	
	No	Yes
Characteristics	n=3264	n=386
Worry about COVID-19, n (%)[d]		
Not at all	142 (4.3)	22 (5.8)
Not very worried	691 (21.2)	76 (19.8)
Somewhat worried	1529 (46.8)	177 (45.8)
Very worried	468 (14.3)	63 (16.4)

Values of polytomous variables may not sum to 100% because of rounding or missingness.

BMI, body mass index; *GAD-2*, Generalized Anxiety Disorder 2-item; *IQR*, interquartile range; *PHQ-2*, Patient Health Questionnaire-2.

[a] Not age-standardized; age in 2020; [b] Hysterectomy or ultrasound-confirmed uterine fibroids; [c] Defined as failure to conceive after 12 months of attempting; [d] Measured at COVID substudy baseline (April–August 2020), n=3283; [e] Defined as physically working at a site providing clinical care.

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Results in the context of what is known

Although men have double the risk of COVID-19 severity and mortality,[35,36] SARS-CoV-2–infected women are estimated to have 50% higher risk of developing long COVID-19 compared with men.[12,14,15] There have been calls for quantification and scientific exploration of the changes in symptoms and the impact of altered disease management for those with gynecologic disorders during the pandemic,[37,38] but limited studies have examined those with existing gynecologic conditions as a group at higher risk for long COVID-19. We found that women with a history of endometriosis had 22% greater risk of long COVID-19, which agreed with one retrospective cohort study analyzing medical record data.[14] This study of a sample of 212,544 women with record of SARS-CoV-2 infection in the United Kingdom found that endometriosis was

TABLE 2
Associations between laparoscopically-confirmed endometriosis and risk of long COVID-19 among participants with self-report of positive SARS-CoV-2 test during follow-up (Nurses' Health Study II [1989–2021] and Nurses' Health Study 3 [2010–2022]), N = 3650

Long COVID-19	Long COVID-19/participants who reported SARS-CoV-2 positive tests	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Defined as having ≥4 wk of symptoms				
Endometriosis				
No	1390/3264	Ref (1.0)	Ref (1.0)	Ref (1.0)
Yes	208/386	1.26 (1.09–1.46)	1.26 (1.09–1.46)	1.22 (1.05–1.42)
Defined as having ≥8 wk of symptoms[a]				
Endometriosis				
No	1166/3171	Ref (1.0)	Ref (1.0)	Ref (1.0)
Yes	187/380	1.33 (1.14–1.55)	1.33 (1.13–1.55)	1.28 (1.09–1.50)
Defined as having ongoing symptoms				
Endometriosis				
No	951/3264	Ref (1.0)	Ref (1.0)	Ref (1.0)
Yes	158/386	1.37 (1.16–1.63)	1.37 (1.15–1.62)	1.32 (1.11–1.58)

RRs were estimated by Poisson regression models. Model 1: adjusted for age, race, and partner's education. Model 2: model 1+smoking status and body mass index. Model 3: model 2+history of asthma, history of hypertension, history of high cholesterol, history of cancer, and history of infertility.

CI, confidence interval; *RR*, relative risk.

[a] Excluded 104 participants whose date from infection had not reached 8 weeks.

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TABLE 3
Associations between laparoscopically-confirmed endometriosis with and without reproductive comorbidities and risk of long COVID (≥4 weeks of symptoms) among participants with self-report of positive SARS-CoV-2 test during follow-up (Nurses' Health Study II [1989–2021] and Nurses' Health Study 3 [2010–2022]), N = 3650

Long COVID-19	Long COVID/participants who reported SARS-CoV-2 positive tests	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Presence of uterine fibroids[a]				
No history of endometriosis	1390/3264	Ref (1.0)	Ref (1.0)	Ref (1.0)
Endometriosis, without history of fibroids	122/233	1.23 (1.02–1.48)	1.23 (1.02–1.48)	1.20 (0.99–1.45)
Endometriosis, with history of fibroids	86/153	1.32 (1.06–1.64)	1.30 (1.05–1.63)	1.26 (1.01–1.57)
P for pairwise test	.73			
History of infertility[b,c]				
No history of endometriosis	1390/3264	Ref (1.0)	Ref (1.0)	Ref (1.0)
Endometriosis, without history of infertility	111/214	1.22 (1.00–1.48)	1.21 (1.00–1.47)	1.20 (0.99–1.46)
Endometriosis, with history of infertility	97/172	1.32 (1.07–1.62)	1.32 (1.07–1.62)	1.31 (1.06–1.61)
P for pairwise test	.55			

RRs were estimated by Poisson regression models. Model 1: adjusted for age, race, and partner's education. Model 2: model 1+smoking status and body mass index. Model 3: model 2+history of asthma, history of hypertension, history of high cholesterol, history of cancer, and history of infertility.

CI, confidence interval; *RR*, relative risk.

[a] Hysterectomy- or ultrasound-confirmed uterine fibroids; [b] Defined as failure to conceive after 12 months of attempting; [c] Did not adjust for history of infertility.

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associated with increased risk of having prolonged/post-COVID-19–associated symptoms at ≥12 weeks (with a remarkably similar adjusted risk ratio of 1.19; 95% CI, 1.11–1.28). However, the prevalence of endometriosis identified by International Classification of Diseases code documentation was low (2.7%; 5727/212,544 women). Therefore, the risk estimate may not be directly comparable with our findings. In addition, the association between endometriosis and long COVID-19 was of a similar magnitude to other established risk factors for long COVID-19, such as asthma, type 2 diabetes mellitus, and hypertension (RR range, 1.1–1.2).[14,24]

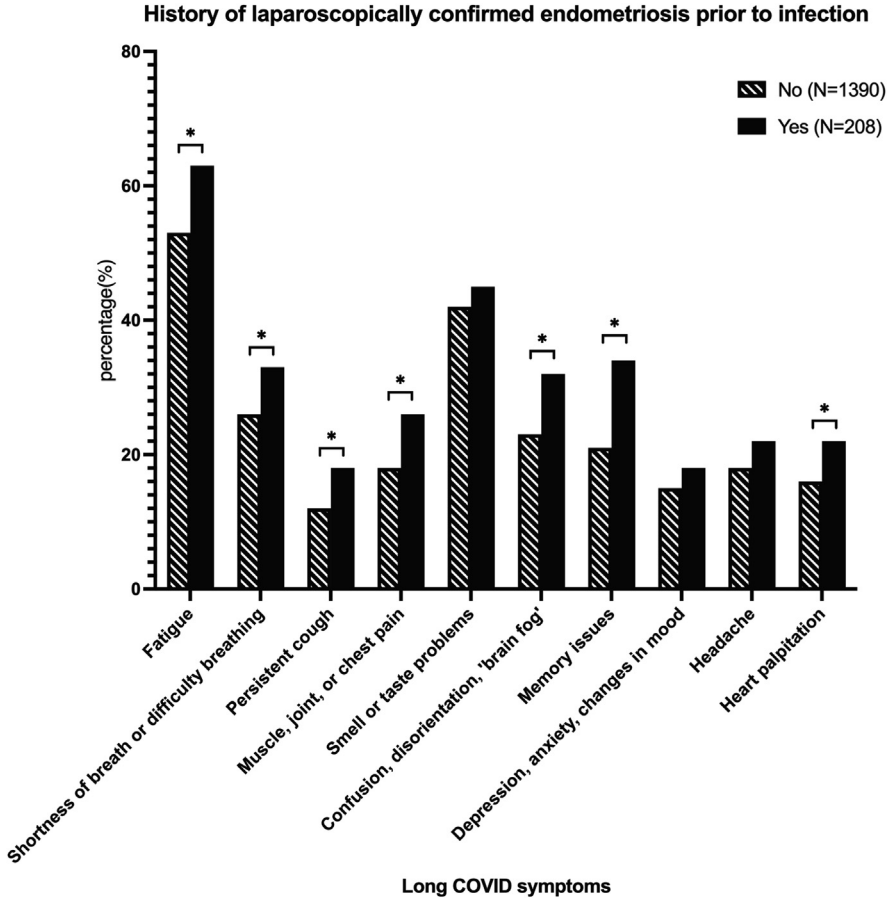
Clinical implications

Endometriosis is characterized by chronic low-grade inflammation and immune dysregulation, resulting in sustained production of proinflammatory cytokines and reactive oxygen species.[10] This mechanism has been implicated in long COVID-19 symptoms, including but not limited to chronic fatigue, stroke, cognitive impairment, cardiac fibrosis, loss of taste and smell, and lung thrombosis.[3] In addition, organs and tissues expressing angiotensin-converting enzyme 2 (ACE2) (the receptor for SARS-CoV-2), such as heart, lung, tongue, and blood vessels, are susceptible to direct damage by the virus itself and inflammation.[3] Because ACE2 is expressed in endometrial tissue, ectopic endometrium may predispose women with endometriosis to multiorgan impairment.[39,40] Moreover, autoimmune antibodies have been linked to both endometriosis and autonomic dysfunction in long COVID-19.[10,13,18] Clotting disorders, a proposed mechanism of long COVID-19,[16] have also been reported among persons with endometriosis.[41,42]

Strengths and limitations

Our study has several limitations. First, this is not a random sample of US women. Our study population predominantly comprised White, middle-aged nurses. However, the study design enhances internal validity because of health professionals' medical knowledge and commitment to research.[21] In addition, it is unlikely that the biological mechanism underlying an association between endometriosis and greater risk of long COVID-19 would differ between nurses and the general population. Second, because of the complexity in diagnosis of endometriosis, our reference group may include women who were asymptomatic or had not yet been diagnosed with endometriosis. However, we expect this percentage to be relatively low and unable to significantly bias the results[43]; we further note that within this study population, the prevalence of history of laparoscopically-confirmed endometriosis was 10%. Third, SARS-CoV-2 infection, vaccination, hospitalization, and long-term symptoms were self-reported. Nevertheless, the validity of self-reported health information was high in these cohorts of medical professionals.[29,44,45] Fourth, symptoms of endometriosis and COVID-19 may overlap, which may have introduced bias. However, results were similar when we excluded women whose only reported prolonged COVID-19 symptoms were pain, depression, and/or fatigue. Fifth, we do not have information on the

FIGURE 2
Long COVID-19 symptoms according to history of endometriosis, N = 1598



Only symptoms with >3% prevalence are listed. *Asterisk* denotes $P<.05$ under chi square test.

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subphenotypic characteristics of endometriosis among these participants,[10,11] which precludes us from testing potential phenotype-specific heterogeneity in the relationship between endometriosis and long COVID-19.

Strengths of our study include a prospective design with long-term follow-up and cohort sustainment long before the pandemic onset, with confirmation of endometriosis by laparoscopy and with extremely high validity. Incident SARS-CoV-2 infections, hospitalizations, and vaccinations were rigorously ascertained during an active phase of the pandemic. We were also able to investigate the potential effect of pandemic-related stress, severity of acute phase disease, and other behavioral and reproductive risk factors using validated measures.

Conclusions

In summary, our findings suggest that those with endometriosis are a group at higher risk of developing long COVID-19 and potentially daily life impairment owing to long COVID-19. Healthcare providers should consider informing endometriosis patients of their increased risk of long COVID-19 and the benefits of preventive measures such as vaccines. Future research should focus on the underlying mechanism linking endometriosis with long COVID-19, and whether management of endometriosis may reduce the risk for long COVID-19 and other postinfection syndromes. ■

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SUPPLEMENTAL TABLE 1

Associations between laparoscopically-confirmed endometriosis and risk of long COVID-19 (≥4 weeks of long-term symptoms) among participants with self-report of positive SARS-CoV-2 test during follow-up, stratified by age at baseline (Nurses' Health Study II [1989–2021] and Nurses' Health Study 3 [2010–2022]), N = 3650

	Age <50 (n=1199)		Age ≥50 (n=2451)	
Long COVID-19	Long COVID/participants who reported SARS-CoV-2 positive tests	Multivariable model RR (95% CI)	Long COVID/ positive tests	Multivariable model RR (95% CI)
Laparoscopically-confirmed endometriosis				
No	484/1125	Ref (1.0)	906/2139	Ref (1.0)
Yes	45/74	1.37 (1.00–1.88)	163/312	1.19 (1.01–1.41)
P interaction	.39			

RRs were estimated by Poisson regression models. Models adjusted for age, race, and partner's education, smoking status, body mass index, history of diabetes mellitus, history of asthma, history of hypertension, history of high cholesterol, history of cancer, and history of infertility.

CI, confidence interval; *RR*, relative risk.

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SUPPLEMENTAL TABLE 2

Associations between endometriosis and risk of long COVID-19 (>4 weeks of symptoms) among participants with self-report of positive SARS-CoV-2 test during follow-up, N = 3650

Sensitivity analyses	Long COVID-19/ participants who reported SARS-CoV-2 positive tests	Multivariable model RR (95% CI)
Main analysis		
Endometriosis		
No	1390/3264	Ref (1.0)
Yes	208/386	1.22 (1.05–1.42)
Included self-reported endometriosis without laparoscopy confirmation		
Endometriosis		
No	1390/3264	Ref (1.0)
Yes	279/509	1.25 (1.09–1.42)
Included self-presumed COVID-19 cases without confirmation tests		
Endometriosis		
No	1817/4552	Ref (1.0)
Yes	286/573	1.21 (1.07–1.38)
Excluding 132 participants reporting only fatigue, depression, headache, and muscle pain		
Endometriosis		
No	1277/3151	Ref (1.0)
Yes	189/367	1.22 (1.04–1.42)
Additionally adjusted for hospitalization because of COVID-19		
Endometriosis		
No	1390/3264	Ref (1.0)
Yes	208/386	1.21 (1.04–1.40)
Additionally adjusted for vaccination status by time of infection		
Endometriosis		
No	1390/3264	Ref (1.0)
Yes	208/386	1.23 (1.06–1.43)
Restricted to SARS-CoV-2 infections before COVID-19 vaccination authorization[a]		
Endometriosis		
No	946/2049	Ref (1.0)
Yes	135/243	1.19 (0.98–1.43)
Excluding potential persons infected with Omicron variant[b]		
Endometriosis		

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SUPPLEMENTAL TABLE 2

Associations between endometriosis and risk of long COVID-19 (>4 weeks of symptoms) among participants with self-report of positive SARS-CoV-2 test during follow-up, N = 3650 *(continued)*

Sensitivity analyses	Long COVID-19/ participants who reported SARS-CoV-2 positive tests	Multivariable model RR (95% CI)
No	1361/3117	Ref (1.0)
Yes	206/377	1.22 (1.05–1.42)
Multiple imputations for 337 persons who did not respond to the long COVID-19 question[c]		
Endometriosis		
No	NA	Ref (1.0)
Yes	NA	1.24 (1.08–1.43)
Treating all missing long COVID-19 status as endometriosis exposed		
Endometriosis		
No	1390/3560	Ref (1.0)
Yes	208/417	1.25 (1.07–1.45)
Treating all missing long COVID-19 status as no endometriosis		
Endometriosis	1686/3560	Ref (1.0)
No	239/417	1.16 (1.01–1.34)
Yes		
Multiple imputations for missing covariates		
Endometriosis		
No	1390/3264	Ref (1.0)
Yes	208/386	1.22 (1.05–1.41)
Complete case analysis[d]		
Endometriosis		
No	1369/3214	Ref (1.0)
Yes	105/381	1.22 (1.05–1.42)

RRs were estimated by Poisson regression models. Models adjusted for age, race, and partner's education, smoking status, body mass index, history of diabetes mellitus, history of asthma, history of hypertension, history of high cholesterol, history of cancer, and history of infertility.

CI, confidence interval; *RR*, relative risk.

[a] Excluding infections after December 11, 2020; [b] Excluding infections after November 1, 2021; [c] Multiple imputation was performed with fully conditional specification using 20 imputed data sets; [d] Restricting to 3595 participants with no missingness on any of the covariates.

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SUPPLEMENTAL TABLE 3

Associations between endometriosis and risk of long COVID-19 (>4 weeks of symptoms) among participants with self-report of positive SARS-CoV-2 test during follow-up and who participated in the COVID-19 substudy, N = 3155

Sensitivity analyses	Long COVID-19/participants who reported SARS-CoV-2 positive tests	Multivariable model RR (95% CI)
Main analysis		
Endometriosis		
No	1212/2804	Ref (1.0)
Yes	189/351	1.20 (1.03–1.41)
Additionally adjusted for healthcare worker status, depressive symptoms, anxiety symptoms, and worry about COVID-19[a]		
Endometriosis		
No	1212/2804	Ref (1.0)
Yes	189/351	1.19 (1.02–1.39)

CI, confidence interval; *RR*, relative risk.

[a] Depressive symptoms were measured by the Patient Health Questionnaire-2. Anxiety symptoms were measured by the Generalized Anxiety Disorder 2-item.

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